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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/390,634	PRICE ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *176-177, 180, 183-189, 192, 195-201, 204-214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 276, 278, 280-281 and 282* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims pending in the application are 176,177,180,183-189,192,195-201,204-214,217-223,226-240,243-249,251-253,255-265,268-274,276,278 and 280-282.

DETAILED ACTION

Applicant's amendment to the claims filed on March 26, 2007 has been received and entered. Claims 176, 184-187, 196-199, 210, 218-221, 232, 249, 251, 253, 255, 259-262, 263, 274, 276, 278 and 280 have been amended, while claims 1-175, 178-179, 181-182, 190-191, 193-194, 196-199, 202-203, 212-213, 215-216, 224-225, 241-242, 250, 254, 266-267, 275, 277 and 279 have been canceled.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 03/26/2007 has been entered.

Claims 176-177, 180, 183-189, 192, 195-201, 204-214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 276, 278, 280-281 and 282 are under consideration.

Claim Rejections - 35 USC § 112

Claims 176-201,204-223,226-241,243-265, 268-282 rejected under 35 U.S.C. 112, first paragraph is withdrawn in view of amendments to the claims limiting to a enabled composition of mouse embryonic stem cells and serum-free media capable of

preventing differentiations of mouse embryonic stem cells, and the methods of use of said composition.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 176-177, 180, 183-189, 192, 195-201, 204-214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 276, 278, 280-281 and 282 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 176, 210, 232, 249, 251, 253, 255, 263, 274, 276, 278 and 280 are unclear because the claims recite a limitation that serum free culture medium is capable of preventing differentiation. It is unclear whether these characteristics actually occur or that the medium could potentially prevent differentiation. "Capable of" implies a latent property. Therefore, it is unclear if the latent property is ever obtained. Claims 177, 180, 183-189, 192, 195-201, 204-209, 211-214, 217-223, 226-2331, 233-240, 243-248, 252, 256-262, 264-265, 268-273, 281 and 282 directly or indirectly depend in independent claims 176, 210, 232, 249, 251, 253, 255, 263, 274, 276, 278 and 280. Appropriate correction is required.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 176-177, 180, 183-189, 192, 195-201, 204-214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 276, 278, 280-281 and 282 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Ponting (US Patent 5,405,772, IDS), Gibco BRL Products and Reference Guide ((1997) Chapters 5 and 8, art of record) and Atsumi et al. (Develop. Growth & Differ. 35(1):81-87, 1993, art of record).

Applicants argue that cited references: (i) fail to provide all elements of the claims; 2) fails to provide any motivation or suggestion to combine the elements of the present claims in the manner claimed; and 3) fails to provide a reasonable expectation of success for combining the claimed elements to arrive at the claimed invention. Applicants assert that Ponting et al do not teach medium capable of preventing

differentiation of mouse ES cell during expansion (see page 18 of the argument). Applicants arguments have been fully considered, but found not persuasive.

With respect to applicants argument that none of the reference teach serum free cell culture medium capable of preventing differentiation of mouse ES cell during expansion. It is emphasized that limitation capable of preventing differentiation implies a latent property, and instant claims fail to suggest whether this property is ever obtained. In addition, even if claims are amended to recite this property, it is noted that preventing differentiation of ES cells is not obtained by synthetic serum rather it is obtained by providing LIF to the culture which is clearly known in the prior art as evidenced by Atsumi. In response to applicant's arguments against the references individually that neither Ponting teaches nor suggest cell culture medium that prevents differentiation of mouse ES cell (see page 19), one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). To the contrary, each reference provides conditions to maintain ES cells in an undifferentiated state. As stated in previous office action serum causes differentiation and not the basal media. Ponting provided a synthetic media and guidance to obtain a media that would not differentiate ES cells. Moreover, it is noted that other factors besides the generality of the media, such as the presence of LIF for mice is feeder free conditions, that provides the condition wherein ES cells do not differentiate. The combination of cited references provides the necessary guidance and details for providing a synthetic serum supplement. GIBCO

reference provided specific compounds to be added to the media such as LIF, SF, lipid-poor albumin, iron-saturated transferring, it is noted that these elements were commercially available at the time of filing (for example page 15 of the instant specification) and also evidenced by Gibco BRL Products and Reference Guide. It is noted that Ponting teaches that the media should be as defined as possible and optimized for a given cell type, therefore one of ordinary skill in the art would be motivated to use and test the various forms of these components for their specific affects on the cells in culture. For example, lipid-poor albumin provides a more defined source of albumin, lacking lipids that could affect the cells. Moreover, Ponting teaches that the components can be natural or synthetic (column 11, lines 65-68), wherein a synthetic component would represent a more defined molecule free from potential contaminants that may be present in naturally isolated sources. Applicants further argue that Atsumi et al do not cure the deficiency of Ponting. As noted before, the art provides evidence that at the time of filing and issuance of Ponting serum-free conditions for culturing embryonic stem cells were known and used (see also Atsumi et al). Atsumi et al teach to use of a serum supplement serum-free media that are obtained as a conditioned media. Using such media, Atsumi et al. were able to define specific factors supplied by the feeder cells in order to make a complete serum-free media. Ponting clearly provides motivation of the specific embodiments required to make a synthetic serum supplement. While Ponting does not specifically disclose all the specific components listed in the claims, the use of these components would be obvious because they are factors commonly used in cell culture. Importantly, upon review of the

present specification, there is no specific teaching that any one of the components recited or encompassed by the instant claims provides any unexpected affect on the cultured cells that would not have been readily known in the art, such as the use of LIF to maintain embryonic stem cells in culture. The level of knowledge and skill in the art for culturing cells is high, and there would be a reasonable motivation and expectation of success to use specific components from various sources as provided by Ponting, Atsumi and GIBCO catalogue to provide for a more defined and optimized media.

Claims 176-177, 180, 183-189, 192, 195-201, 204-214, 217-223, 226-240, 243-249, 251-253, 255-265, 268-274, 276, 278, 280-281 and 282 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ponting (US Patent 5,405,772, art of record), Gibco BRL Products and Reference Guide ((1997) Chapters 5 and 8, art of record), Atsumi et al. (Develop. Growth & Differ. 35(1): 81-87, 1993, art of record) and Nichols et al (Exp Cell Res. 1994; 215(1):237-9, IDS).

Ponting teaches a medium for long-term proliferation and development of cells. Beyond basal media commercially available, Ponting provides guidance for obtaining serum free media (starting at column 14, line 57). Ponting teach specific components and preferred ranges thereof to include in the media (see for example Table in columns 12 and 13). Ponting teaches that the media can contain albumin (e.g. human or bovine), transferrin (e.g. human or bovine), growth factors, vitamins, antioxidants, insulin and various trace elements (see columns 9-10, tables and reduction to practice in working examples). Ponting teaches that the media disclosed can be used to culture a variety of

cell types including embryonic stem cells (column 8, lines 13-15) including specific reference to known mouse embryonic stem cell lines. Further, Ponting teaches that general culturing methods known in the art can be used to culture a particular cell type, such as providing a feeder cell layer (column 8, lines 30-37). Finally, Ponting teaches that the cells can be used in a variety of methods including in the production of proteins in culture (column 16, lines 21-31 and 45-64) and methods of differentiation (see column 8, lines 32-42, lines 61-69 and working examples). Additionally, it is noted that media composition can be in a frozen state preparations. The invention disclosed by Ponting is to provide a completely defined media (column 1). Ponting teaches that the disclosed media can be used for variety of cell types and that the defined media 'makes possible the precise determination of the effect of a known molecule" (column 7, lines 44-50). Further, Ponting teaches that in determining the effective amount of any of the constituent components experimentation by methods known to a cell culturist would have to be done (bridging columns 8-9 and generally supported by the working examples). Finally, Ponting teaches that specific conditions for culturing a particular cell type would have to be adapted by substituting the serum-supplement to the methods and materials known in the art that would have been used for any particular cell type (starting in column 15, section E). Though Ponting does not specifically teach to use factors such as LIF, iron-saturated transferrin or lipid poor and recombinant albumin, these factors were readily available at the time of filing and used in cell culturing. For example, at the time of filing it was well known that mouse embryonic stem cells required LIF in the culture media to efficiently maintain their undifferentiated state during

culturing, therefore, it would be obvious to include this factor in the propagation of embryonic stem cells. Further, if the mouse ES cells were to be used in methods of differentiation or if the culture was human embryonic stem cells that were known not to be responsive to the presence or absence of LIF, this factor would be excluded from the media. The remaining embodiments of addition of specific forms of albumin and transferrin, for example iron-saturated transferrin or lipid poor and recombinant albumin, as well as specific growth factors necessary for maintaining mouse embryonic stem cells in an undifferentiated state, such as the use of LIF. The use of these components would be obvious because they are factors commonly used in cell culture. With respect to the specific compounds to be added to the media such as LIF, SF, lipid-poor albumin, iron-saturated transferring, it is noted that these elements were commercially available at the time of filing of this application (for example page 15 of the instant specification) and also evidenced by Gibco BRL Products and Reference Guide. Ponting differed from claimed invention by not specifically disclosing that serum free medium contained other differentiation inhibitory agent as listed in the claims.

Atsumi et al. provides evidence that serum-free conditions for culturing embryonic stem cells were known and used. Atsumi et al teach to use as a serum supplement serum-free media that are obtained as a conditioned media. Using such media, Atsumi et al were able to define specific factors supplied by the feeder cells in order to make a complete serum-free media. Specifically It is noted that Atsumi et al disclose addition of LIF to the serum free medium to culture mouse ES cells (10^5) increases the proliferation of ES cells in serum free medium (see Figure 5 and page 85,

col. 1, para. 1). Astumi et al differed from claimed invention by not disclosing other components in serum free medium.

Prior to instant invention, Nichols teaches mouse blastocysts plated in non supplemented medium in the absence of a feeder layer differentiate and do not give rise to ES cells, while a cell line could be established in presence of LIF. It is noted that presence of DIA/LIF, oncostatin M and CNTF prevented differentiation of ES cells and withdrawal of these cytokine resulted in differentiation of the cells (see page 238, col. 1, results, para. 1). Although, medium disclosed by Nichols differed from claimed invention as it contained serum, however, it is apparent from the teaching that presence of instant cytokine prevented differentiation of mouse ES cells. However, Nichols differed from claimed invention by not disclosing a serum free medium.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the composition or products of manufacture comprising cell culture medium and medium supplements of Ponting by altering the types of supplements to be included in the basal medium formulation as disclosed by Atsumi or Nichols. Ponting taught that the media should be as defined as possible and optimized for a given cell type, therefore one would be motivated to use and test the various forms of these components for their specific affects on the cells in culture. For example, lipid-poor albumin provides a more defined source of albumin, lacking lipids that could affect the cells. Moreover, Ponting teaches that the components can be natural or synthetic (column 11, lines 65-68), wherein a synthetic component would represent a more defined molecule free from potential contaminants that may be

present in naturally isolated sources. One of skill in the art would have been motivated to provide a product of manufacture containing a combination of serum-free medium and serum-free supplements optimized for expanding mouse ES cells in view of the disadvantages of using serum and the advantages of using serum-free medium formulations for culturing ES cells, as disclosed by Ponting. In addition, freezing such formulations/supplements for shipping and storage is well known as evidenced by GIBCOBRL Catalogue disclosing maintaining compositions containing nutrients in the frozen state enhances the stability of such compositions (supra). One who would practiced the invention would have had reasonable expectation of success because Ponting had already described in determining the effective amount of any of the constituent components experimentation by methods known to a cell culturist would have to be done (bridging columns 8-9 and generally supported by the working examples). Atsumi provided guidance that addition of LIF to the serum free medium to culture mouse ES cells increases the proliferation of ES cells, while Nichols provided guidance in terms of presence of DIA/LIF, oncostatin M and CNTF prevents differentiation of ES cells and withdrawal of these cytokine result in differentiation of the ES cells. Furthermore, GIBCO BRL Catalogue provided indicated that serum-free medium supplements are shipped frozen and should be stored frozen to insure quality or to sustain optimal performance of the products. Therefore, given that serum free medium comprising lipid rich serum albumin and other differentiation inhibiting agent such as LIF, oncostatin M and CNTF were available for use to culture ES cells as per the teachings of Ponting and Atsumi it would have obvious for to one of ordinary skill in

the art to optimize the serum free culture medium for optimal growth of mouse ES cells as disclosed in the instant application.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Maurer ("Animal Cell Culture, A Practical Approach", pages 13-31, 1986, IDS) Maurer teaches commercially available serum-free media and supplements which are available for optimizing mammalian cell cultures (see page 28-29, and Table 3) including the use of serum-substitutes, such as insulin, transferrin, growth factors, and hormones, for replacing the serum, as well as other supplements such as trace elements (see, page 25).

No Claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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